

Review Article

An evidence-based review of Dopamine receptor agonists in the treatment of Parkinson's disease

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ABSTRACT

Apomorphine and certain ergot alkaloids (bromocriptine, lisuride and pergolide) have been available for several decades; for the last few years, they were joined by newer dopamine agonists (cabergoline, pramipexole and ropinirole) most of them are non-ergolines. Each of these dopamine agonists has its own pharmacological characteristics and occupies a place in the pharmacotherapy of Parkinson's disease. In this evidence-based review, emphasis is put on the clinical efficacy of dopamine agonists in early and advanced Parkinson's disease, and where possible comparative evidence regarding their efficacy and safety is provided. In addition, their clinical pharmacokinetics, adverse effect profiles and most relevant interactions will be summarized.

Saudi Med J 2002; Vol. 23 (10): 1165-1175

The motor dysfunction characterizing Parkinson's disease (PD) is caused by primary degeneration of nigral dopaminergic neurons of the pars compacta. Levodopa (L-dopa) reverses parkinsonian motor deficit through its conversion to dopamine and remains the most effective drug for the treatment of PD. Despite this, chronic L-dopa therapy is associated with long-term side effects ('wearing-off' and 'on-off' fluctuations, freezing, 'early-morning' dystonia and dyskinesia) and neuropsychiatric manifestations.¹ In an attempt to overcome several of these limitations new classes of antiparkinsonian drugs like synthetic dopamine agonists (DA), monoamine oxidase-B and catechol-O-methyltransferase inhibitors have been developed. Centrally-acting DA stimulate dopamine receptors directly. By acting at the striatal postsynaptic dopamine receptors, DA bypass the degenerating presynaptic neuron from the substantia nigra and act independent of the synthetic dopaminergic enzyme system. Some additional advantages supportive of the use of DA for the treatment of PD include

decreased auto-oxidation of dopamine resulting from exogenous L-dopa thus avoiding the generation of free radicals which may be involved in neuronal degeneration; lack of competition from dietary amino acids for gastrointestinal uptake or blood-brain transfer; no need for storage in, biotransformation by, or release from currently degenerating neurons; and an increased reliability of dose-by-dose effects.² In addition, since DA have long half-lives they have the potential to exert more long lasting effects. Dopamine agonists can be highly specific to subpopulations of dopamine receptors and devoid of adverse effects caused by generalized dopaminergic stimulation and properties related to norepinephrine and serotonin. Receptor cloning has led to the discovery of at least 5 distinct dopamine (D) receptor subtypes (D₁ - D₅) and are usually classified as D₁ like (D₁, D₅) and D₂ like (D₂, D₃, D₄).³ These receptors differ in their distribution within the brain and in their pharmacological properties. Dopamine one (D₁) receptors are positively linked to adenylate

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cyclase and are located predominately in intrastriatal neurons. Dopamine 2 receptors are not linked or are negatively linked to adenylate cyclase and are located predominately in axons of a descending corticostriatal tract. Both D₁ and D₂ receptors are thought to be postsynaptic. Dopamine 3 receptors are partially pre- and partially postsynaptic. Because no pharmacological ligands that distinguish among each subtype of dopamine receptor are available, the exact relationship of receptor profiles of DA and their clinical response remains uncertain. However, the role of postsynaptic D₂ receptor agonism in reversing motor deficit in experimental as well as clinical conditions is well documented.⁴ Presynaptic D₂ receptor stimulation may be related to neuroprotective effects.⁵ Considerable controversy exists over the role of D₁ receptors. There is some evidence that D₁ receptors contribute to dyskinesias, may provide additional symptomatic effects, or may produce a combination of the 2 effects.⁶ Most of the DA currently employed for the treatment of PD are D₂ DA with or without activity on D₁ receptors. Newer DA ropinirole and pramipexole show some selective agonistic activity at D₃ receptors.² **Table 1** summarizes the affinity to monoamine receptors of various DA currently used to treat PD. There has been continued interest in DA either as monotherapy or as adjuvant therapy to L-dopa due to the high prevalence of adverse reactions and decreased efficacy of L-dopa when patients have received long-term treatment. Dopamine agonists are also being used as adjunctive therapy to reduce the dose of L-dopa required. It is thought that reducing the L-dopa dose will decrease the adverse reactions to L-dopa. Interest in DA has also focused on their potential role in neuroprotection.⁵ Treatment with DA may alter the disease course in PD by preventing or reducing pre- and post-synaptic changes. Firstly, the reduction in the amount of L-dopa used for treatment decreases the levels of oxygen free radicals generated by the oxidative metabolism of dopamine.⁵ Secondly, DA such as bromocriptine, pergolide, ropinirole and pramipexole have been shown to act as free radical scavengers against hydroxyl radicals, nitric oxide radicals and to have antioxidant effects.^{5,7,8}

During the last 3 decades, numerous DA have been the subject of evaluation in the treatment of PD in its various clinical stages. Some of them (for example, mesulergine, lergotril and 4-propyl-9-hydroxynaphthoxazine [PHNO]) have not even made it to the clinical stage due to toxicity.⁹ Dopamine agonists can be structurally divided into ergot alkaloids (bromocriptine, cabergoline, pergolide and lisuride), non-ergolines (piribedil, pramipexole and ropinirole) and aporphines (apomorphine). The pharmacokinetic properties of DA are summarized in **Table 2**. Dose equivalents amongst the DA is roughly 600mg of L-dopa/peripheral, decarboxylase inhibitor is equivalent to 30 mg of bromocriptine, 3.0

mg of pergolide, 3.0 mg lisuride, 15 mg of ropinirole and 4.5 mg of pramipexole.

The purpose of this article is to provide an evidenced-based review on the clinical efficacy of the currently available DA. In addition, their clinical pharmacokinetics, adverse effect profiles and most relevant interactions will be summarized.

Ergot dopamine agonists. Bromocriptine. Bromocriptine has been employed both as monotherapy and as adjuvant therapy with L-dopa. Bromocriptine is a strong agonist at D₂ receptors and a weak antagonist at D₁ receptors.⁹ Besides, its effect on dopamine receptors it also blocks 5-HT receptors and α -adrenoceptors. Bromocriptine was reported to have a potential neuroprotective effect.⁵ Low doses of 5 - 30 mg/day have been shown to have a modest antiparkinsonian effect; higher doses of 30-100 mg/day have a better effect but cause more adverse events.¹⁰ As an adjuvant to L-dopa, doses of bromocriptine up to 52 mg/day have been used. No clear relationship has been established between magnitude or duration of antiparkinsonian response and the plasma levels of bromocriptine.¹⁰ In general, the initial antiparkinsonian response was observed after 30-90 minutes after dose intake, is maximal at approximately 2 hours and lasts 3-5 hours.

Numerous clinical trials have evaluated bromocriptine in monotherapy or as adjunct to L-dopa in early PD. These studies need to be interpreted with caution due to the limited number of patients, high drop out rates (up to 50%) and methodological issues. In addition, these early studies do not allow comparison with the currently used PD scales. Nevertheless, the results indicate that bromocriptine has a modest antiparkinsonian effect, which is inferior to that of L-dopa but treatment with bromocriptine results in significantly less dyskinesia and dystonia.^{10,11} However, the lack of efficacy (30% non-responders), high incidence of adverse effects and development of tolerance after 6 months limits the use of bromocriptine monotherapy.^{11,12} A long-term (5-year) study revealed that a minority (<10%) of patients could be managed on bromocriptine monotherapy for more than 3 years, but these patients did not develop dyskinesias or wearing-off failure until L-dopa was added to their regimen (**Table 3**).¹² A long-term (3 years) study comparing bromocriptine monotherapy with L-dopa monotherapy and L-dopa plus selegiline revealed that bromocriptine monotherapy was significantly less effective and resulted in a higher rate of adverse effects than either L-dopa monotherapy or L-dopa with selegiline.¹¹ Furthermore, the efficacy of bromocriptine monotherapy gradually waned after reaching a peak in the first 6 months. However, it did not go unnoticed that bromocriptine monotherapy caused fewer dyskinesias and motor fluctuations (2-5%) compared to both L-dopa-treated groups (27-35%). The early use of bromocriptine (15 mg/day or

more) as adjunct to L-dopa in delaying or preventing the onset of motor response fluctuations has been a matter of debate.^{13,14} Some studies indicated that early use of combined bromocriptine and L-dopa decrease the incidence of wearing-off (-10 to -30%) and dyskinesias (-40%) and allows the L-dopa dose to be reduced by 10-30%.^{12,13} These effects were observed with bromocriptine doses above 15 mg/day. Low dose bromocriptine combined with L-dopa provide a comparable therapeutic response to L-dopa monotherapy but with fewer end-of-dose deterioration and peak-dose dyskinesias (Table 3).¹² Review of clinical trials of bromocriptine as adjunct to L-dopa in advanced PD indicated that this regimen improved motor performance in up to 70% of patients.¹⁰ In addition, 70% of patients with motor response fluctuations had an improvement in "on" time and reduction in dyskinesia. However, in the majority of patients, the beneficial effects of bromocriptine waned after 3 years. Similar to previous studies, the number of adverse drug reactions resulted in a high drop out rate (up to 40%). The most relevant double-blind placebo-controlled trial of bromocriptine treatment in advanced PD is given in Table 4. Common adverse effects of bromocriptine include mental changes for example, hallucinations, paranoia, somnolence (including excessive daytime sleepiness and sleep attacks) and confusion (often more severe than seen with L-dopa), orthostatic hypotension, dyskinesias and gastrointestinal disturbances (nausea).¹⁵ Long-term adverse effects include fibrotic reactions and digital vasospasm (ergotism).¹⁶ Interactions with bromocriptine include increased bromocriptine toxicity when combined with macrolide antibiotics (for example erythromycin) or alcohol.^{15,17} Hypertension, cerebral hypertension and seizures have been reported when concurrently taking sympathomimetics.¹⁵ Bromocriptine should not be taken together with other ergot alkaloids or with dopamine antagonists such as phenothiazines.

Pergolide. Pergolide has a therapeutic effect and adverse reaction profile similar to that of bromocriptine. Pergolide's therapeutic effect is based on its agonist activity on D₂ receptors.¹⁸ In addition, it also has a partial agonist activity on D₁ receptors and has an affinity for D₃ receptors. Like bromocriptine, pergolide also appears to be neuroprotective.¹⁹ Pergolide is considered to be superior to bromocriptine due to its pharmacokinetic parameters. The dose of pergolide commonly used ranges between 1.5-3.0 mg per day. The maximal antiparkinsonian effect after administration of the drug is 1-2 hours and lasts for several hours.¹⁸ Pergolide monotherapy has been used in patients no longer benefiting from bromocriptine and as adjuvant therapy when L-dopa becomes less effective or gives adverse effects.²⁰ The only reported multicenter, randomized, double-blind, parallel-group study of pergolide monotherapy versus placebo showed a

highly significant greater percentage of responders (defined as a 30% decrease in Unified Parkinson's Disease Rating Scale [UPDRS] motor score at end-point) compared with placebo (Table 3).²¹ An analysis of 6 studies²⁰ (161 patients) in which pergolide was used as add-on to L-dopa revealed that 74% of patients showed an improvement in "on" time and 35% were able to decrease the L-dopa dose. However, 24% discontinued pergolide treatment due to troublesome adverse effects. These adverse reactions were primarily dyskinesias (resulting from a potentiation of dopaminergic side effects of L-dopa), mental disturbances, hepatotoxicity and cardiovascular arrhythmias.²² Small scale long-term (16 months) studies²³⁻²⁶ involving 66 patients all demonstrated initial improvement with the addition of pergolide, but 38% of patients eventually deteriorated.

In advanced PD, a prospective, double-blind, placebo-controlled study of pergolide as adjunctive therapy to L-dopa showed improvement of motor function, activities of daily living and reduction of motor fluctuations (Table 4).²⁷ In addition, pergolide proved to have a significant L-dopa sparing effect. Reducing the L-dopa dosage effectively controlled the high rate of dyskinesia in the pergolide group. The long-term use of pergolide as add-on to L-dopa in late stage PD shows that after a period of initial improvement (lasting up to one year), the beneficial effect fades slowly in many patients. Only 25% of patients have sustained improvement for 2 years. Across these studies improvement of "on" time seems to be consistent.^{28,29} A number of studies compared the clinical efficacy and safety of bromocriptine and pergolide. Similar responses to the 2 drugs were reported in one study.³⁰ In another study (25 patients), treatment was initiated with bromocriptine and later on switched to pergolide.²⁰ It was found that pergolide maintained efficacy longer than bromocriptine. Cochrane meta analysis of controlled studies of the adjunctive use of DA in PD has shown that pergolide is superior to bromocriptine in reducing motor impairment and disability.³¹ However, insufficient evidence is available to draw any conclusions regarding L-dopa-induced motor complications. Furthermore, no significant differences between both DA are seen in L-dopa dose reduction, adverse events or drop outs. Pergolide's main adverse effects are mental disturbances including hallucinations, dyskinesias, somnolence (including excessive daytime sleepiness and sleep attacks), insomnia and gastrointestinal disturbances.¹⁸

Lisuride. Lisuride stimulates postsynaptic D₂ receptors with a higher affinity than bromocriptine.⁹ It is also a mild agonist/partial antagonist on D₁ receptors and has a high affinity for serotonin receptors. The high saline and water solubility of lisuride allows it to be used for injection or ambulatory infusion pumps (0.3-1.0 mg/hour

intravenous or 1-2 mg/day subcutaneous [SC]).³² The commonly used oral dose ranges between 1-5 mg/day in divided doses. Lisuride has been tried as monotherapy in doses of 0.4-5.0 mg/day for PD and also as adjunct therapy with L-dopa. Parkinsonian symptoms improve within 5 minutes after intravenous administration of lisuride (0.10-0.15 mg) and continues up to 3 hours.² Retrospective analysis of 7 studies³³ (315 patients) in which lisuride was evaluated revealed that 11% of patients could be controlled with lisuride monotherapy. Seventy percent of patients improved and 23% had adverse reactions which lead to discontinuation of the lisuride treatment. Another study revealed that only a small number of patients could be maintained on lisuride monotherapy (Table 3).³⁴ Although combination of lisuride with L-dopa caused a significant decrease in L-dopa requirements and significantly decreased and delayed the onset of motor fluctuations, more adverse effects were observed with lisuride monotherapy leading to withdrawal of the drug.

In advanced PD, lisuride was evaluated in 20 patients who were no longer responsive to L-dopa, including 14 patients with 'on-off' phenomena (Table 4).³⁵ Every patient who completed the study improved significantly (35% decrease in total PD disability score). Fifty percent patients (5 out of 10), who received further treatment with lisuride for one year or more, had no decline in efficacy. Intravenous infusions of lisuride as add-on to L-dopa can significantly reduce daily oscillations in motor performance without increase in dyskinesia.³⁶ Crossover studies comparing responses to lisuride and bromocriptine showed that bromocriptine and lisuride were equally effective in reducing motor disability in PD but lisuride was superior at reducing motor oscillations.^{37,38} One study³⁹ (28 patients) compared the efficacy of lisuride and pergolide and showed that both drugs improved symptoms when added to L-dopa treatment and had comparable adverse reactions; however, pergolide was more effective in reducing oscillations. Lisuride's adverse effects include nausea, vomiting, orthostatic hypotension, headache, sedation (including excessive daytime sleepiness and sleep attacks) and increased dyskinesias. The high incidence of psychiatric side effects during parenteral administration of lisuride limits its use.⁴⁰ The peripherally acting dopamine antagonist, domperidone, can be used to control peripheral adverse effects of lisuride. The drug interactions for lisuride are similar to those of bromocriptine. Paradoxical hypertensive crisis and disappearance of orthostatic hypotension have been reported when lisuride was administered concurrently with domperidone which is known to block peripheral D₂ receptors preventing lisuride's action.

Cabergoline. Cabergoline has a high affinity for D₂ receptors with less affinity for D₁.⁴¹ The receptor binding is long lasting, up to 72 hours.⁴² The recommended dosage for cabergoline is initially one mg/day with increments of 0.5-1.0 mg every one or 2 weeks up to the therapeutic dose of 2-6 mg once daily. In addition, the use of cabergoline as monotherapy for early PD, the drug has been evaluated as adjunct therapy with L-dopa in the advanced stages of the disease. A long-term (3 year) study⁴³ in 412 de novo parkinsonian patients who were randomized to receive either L-dopa (800 mg per day) or cabergoline (averaged 3 mg once daily) revealed that the development of motor complications (end-point) was significantly lower in cabergoline-treated patients than in L-dopa recipients (22% versus 34%) (Table 3). Furthermore, the relative risk of developing motor complications during cabergoline treatment was substantially less (> 50%) than with L-dopa. Adverse effects occurred in 31% cabergoline-treated patients and 25% of those treated with L-dopa. The withdrawal rates in the cabergoline group and L-dopa group were almost similar (16% and 13%). It was concluded that early cabergoline therapy significantly delays the onset of severe motor complications. An analysis of several studies⁴⁴ (total 1,500 patients) in which cabergoline (2-10 mg daily) was used as adjunct therapy to L-dopa in advanced PD, cabergoline significantly decreased the "off" time (45% versus 18% for placebo) and the L-dopa dose requirements (18% versus 3% for placebo). Addition of cabergoline improved UPDRS scores by 23% versus 4%. The results of the most relevant study were shown in Table 4. Clinical review of studies⁴⁵ comparing the efficacy and safety of cabergoline therapy versus bromocriptine add-on to L-dopa in patients with advanced PD showed that cabergoline was at least as effective in "off" time reduction, in improving motor impairment and disability. Furthermore, cabergoline produced similar L-dopa dose reduction over the first 3 months of therapy as bromocriptine. Both drugs were equally well tolerated but in association with L-dopa, dyskinesia and confusion were more frequently observed with cabergoline. The most common adverse effects of cabergoline include nausea, vomiting, dyspepsia, gastritis, hypotension, somnolence (including excessive daytime sleepiness and sleep attacks), dizziness and peripheral edema.⁴³

Non-ergoline dopamine agonists.

Pramipexole. Pramipexole has selective D₂ receptors agonistic properties particularly at D₃ receptors.⁴⁶ Dopamine 3 selectivity is probably responsible for its antiparkinsonian and antidepressive activity. In addition, it is claimed that pramipexole has neuroprotective properties,^{47,48} and acts as an agonist on presynaptic dopamine autoreceptors decreasing the synthesis and turnover of endogenous dopamine hence decreasing oxidative stress. In addition to dopamine receptors it also binds

to α_2 -adrenoceptors.⁴⁹ The dose of pramipexole commonly used ranges from 0.5-1.1 mg 3 times a day (tid). Pramipexole's onset of action is seen after 2 hours.⁵⁰ In early and advanced PD, significant and persistent improvement in UPDRS scores have been observed after 1-4 weeks of oral therapy. Pramipexole is used in mild to moderate PD as monotherapy and also as add-on in advanced PD. Two large randomized double-blind placebo-controlled studies of pramipexole monotherapy in early⁵¹ and mild to moderate de novo PD⁵² revealed that pramipexole was significantly better than placebo. In the first study (264 patients) significant relief of symptoms was obtained with pramipexole at doses of 1.5 mg/day or higher. After 10 weeks of pramipexole treatment, patients showed 20% improvement in total UPDRS scores over placebo.⁵¹ Patients treated with doses of 3 mg/day showed the smallest efficacy/tolerability ratio (92% versus 98% in placebo recipients). In the second study⁵² (335 patients), pramipexole significantly improved motor function and 83% of patients were able to remain on pramipexole monotherapy at 6 months (**Table 3**). Recently, a large randomized, double-blind, placebo-controlled trial compared the development of motor complications after pramipexole (0.5 mg tid) versus L-dopa monotherapy (100/25 mg tid).⁵³ At 94 weeks, pramipexole monotherapy significantly reduced the development of motor fluctuations (28% versus 51% in L-dopa group). However, with regard to the mean improvement in total UPDRS score from baseline to 23.5 months L-dopa was superior to pramipexole (9.2 versus 4.5 points). Pramipexole has also been studied as add-on in patients with advanced PD. In a long-term study (32 weeks), 360 patients were treated with doses up to 4.5 mg/day (**Table 4**).⁵⁴ The pramipexole-treated patients were able to reduce their L-dopa dose (27%), improved in parkinsonian symptoms and had up to 30% reduction in "off" time. Discontinuation due to unwanted effects occurred in 24 treated patients and 30 placebo treated patients. Similar findings were reported by Pinter et al.⁵⁵ overall reduction in "off" periods of 12% (14% gain over placebo) resulting in 1.7 more hours "on" time a day and a 37% reduction in mean UPDRS total score (25% gain over placebo). No increase in dyskinesia in pramipexole-treated patients as compared to controls was observed.

In advanced PD, a randomized, double-blind long-term (36 weeks) study (246 patients) suffering from wearing-off phenomenon compared pramipexole (mean daily dose 3.4 mg) with bromocriptine indirectly.⁵⁵ The study was powered to compare each DA with placebo but was not powered to show statistical differences between both DA. According to comparison of the Global Clinical Assessment of efficacy between active treatment groups, there was a trend to significance in favor of pramipexole. Pramipexole has an adverse effect profile associated with peripheral and central dopaminergic

stimulation. In view of its chemical properties it does not have ergot-related adverse effects. Across these clinical trials, psychiatric reactions such as visual hallucinations are the most frequently reported (20-40% compared to 5-15% in the placebo recipients). Other dose-related adverse effects include nausea, dizziness, fatigue, headache, insomnia, constipation and somnolence.⁵⁶ Similar to other DA, sleep attacks or excessive daytime sleepiness have been reported in pramipexole-treated patients resulting in motor vehicle accidents.^{57,58} A recently performed meta analysis of randomized controlled trials⁵⁹ indicated that PD patients taking pramipexole are at a higher risk of experiencing somnolence and sleep attacks than patients taking placebo or L-dopa alone. Predictor risk factors are increasing age, advanced disease and high dose regimens. Drugs like cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine and quinine which are also excreted by renal tubular secretion will decrease the pramipexole clearance by 20% thereby increasing its area under the curve (AUC) and half life.⁶⁰

Piribedil. The non-ergoline DA, piribedil has D₂/D₃ selectivity.⁶¹ Animal experiments indicate that piribedil has a significant activity against bradykinesia, tremor and rigidity. Recently, it was observed that long-term administration of piribedil induced a potent and sustained reversal of motor impairment with less dyskinesia compared with L-dopa.⁶² Data also indicated that in vivo piribedil interacts preferably with dopamine receptors in the substantia nigra and nucleus accumbens.⁶³ Although the first clinical trials⁶⁴⁻⁶⁶ with piribedil dates back to the early 1970s, it was only recently that the drug was rediscovered due to its favorable therapeutic profile, particularly anti-tremor effect.⁶⁷⁻⁶⁹ Piribedil is used in monotherapy and as adjunct to L-dopa. The commonly used dosage in PD ranges from 120-240 mg/day in divided doses. Onset of the antiparkinsonian action is usually observed 2-4 weeks after the initiation of the therapy.⁶⁵ A randomized placebo-controlled study⁶⁷ (6 months) in which piribedil was evaluated as add-on to L-dopa in patients with early PD, the UPDRS III scores were 33% more favorable with piribedil compared to placebo (**Table 3**). Furthermore, the response rate in piribedil-treated patients was 22% higher than in the placebo group (62% versus 40%). No direct comparison is available between piribedil and other DA. Commonly encountered adverse effects are nausea, vomiting, gastric discomfort, anorexia and constipation, dizziness, somnolence (including excessive daytime sleepiness and sleep attacks) and headache. The degree of nausea required certain patients to take piribedil concomitantly with meals or domperidone.^{65,70} Mild hepatotoxicity with alterations in serum alkaline phosphatase and transaminases has been reported.⁶⁵ So far, no drug interaction data are available.

Ropinirole. Ropinirole has a high specificity for the D₂ receptors especially D₂ and D₃ receptors.^{71,72} The usual dose range for ropinirole is 3-8 mg tid. The onset of action and the time to maximum response of oral ropinirole (0.8 mg) are approximately 30 minutes and one hour. The antiparkinsonian effect lasts for approximately 16 hours.⁷³ Ropinirole has been evaluated as monotherapy in patients with mild to moderate PD and also as add-on therapy along with L-dopa. One long-term (6 month) double-blind study comparing ropinirole with placebo in de novo parkinsonian patients reported a 24% improvement in UPDRS score in ropinirole-treated patients (versus 3% improvement in placebo recipients).⁷⁴ Ropinirole-treated patients also required less levodopa supplementation (11%) than did placebo-treated patients (29%). In a 5-year randomized double-blind study (268 patients) ropinirole was compared to L-dopa (**Table 3**).⁷⁵ The average dose of ropinirole was 16.5 mg and L-dopa was 600 mg. The occurrence of dyskinesia (primary endpoint) was significantly lower in the ropinirole group (20% versus 46% for L-dopa) but similarly as in the pramipexole/L-dopa study, improvement as assessed by UPDRS scores was better with L-dopa (one versus 5). Except for slightly increased frequency in somnolence and hallucinations in the ropinirole group there were no differences observed with respect to adverse effects.

In advanced PD, ropinirole was evaluated as adjunct to L-dopa in patients with wearing-off and dyskinesia. In one multicenter double-blind, placebo-controlled parallel, 6-month study (149 patients)⁷⁶ ropinirole was studied as add-on to L-dopa; 35% of the ropinirole (up to 8 mg tid) and 13% of the placebo-treated patients achieved the primary endpoints having a 20% or greater reduction in "off" time and decrease in dose of L-dopa between baseline and final visit (**Table 4**). The most frequently encountered adverse effects in the ropinirole group were dyskinesias, which occurred before reduction in L-dopa. Other adverse effects were similar for ropinirole and placebo groups. A long-term (3 year) double-blind, randomized comparative study⁷⁷ (335 patients) between ropinirole and bromocriptine in with early PD, revealed that patients taking ropinirole (12 mg) alone showed a significant improvement in motor score (31%) compared with 22% in the bromocriptine group (24 mg) alone. Serious adverse effects were encountered in 3% of ropinirole and 7% of bromocriptine patients. Almost one third of the ropinirole-treated and 50% bromocriptine-treated patients withdrew from the study due to the adverse effects. Most common adverse effects of ropinirole which often lead to withdrawal of the drug are nausea and hallucinations.⁷⁸ Other adverse effects include dizziness, somnolence, postural hypotension and dyskinesias. As with other DA, domperidone given

concurrently alleviates some of the peripheral symptoms. Similarly to pramipexole, PD patients taking ropinirole are at higher risk of experiencing somnolence and sleep attacks than patients taking placebo or L-dopa alone.⁵⁹ Drugs such as ciprofloxacin will increase ropinirole's AUC (+84%) through inhibition of CYP1A2. Estrogens can decrease the ropinirole clearance by 36%.⁷⁹

Apomorphine dopamine agonists. Apomorphine is a short-acting agonist with D₁ and D₂ receptor properties. At low doses it acts at presynaptic autoreceptors to inhibit dopamine turnover.⁸⁰ Its very high water solubility made apomorphine suitable for parenteral administration and was the first antiparkinsonian drug to be used subcutaneously.⁸¹ This route of administration avoids the problem of poor bioavailability and allows the use of much smaller doses (0.5-2.0 mg SC) which are not nephrotoxic. Apomorphine is used as add-on to L-dopa or as rescue therapy for severe "off" periods during L-dopa therapy. Apomorphine can be given subcutaneously either in bolus (0.5-3.0 mg) or by constant infusion (4 mg/h for 12-24 hours). Apomorphine can also be used via intranasal, sublingual or rectal route.⁸²⁻⁸⁴ Data seem to indicate that apomorphine may also exert neuroprotective properties in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice.⁸⁵ In patients with advanced PD, the onset of action is observed 5-20 minutes following SC and 30 minutes after sublingual administration of apomorphine.⁸⁶⁻⁸⁹ The duration of the response to a single subcutaneously administered dose is inversely related to the stage of the disease: 51 minutes in early PD and 29 minutes in advanced PD.⁸⁰ Sublingual administration⁹⁰ of a single dose of apomorphine provides a prolonged duration of action (128 minutes). Long-term administration prolongs the duration of action (0.6-2.5 hours).^{88,91} A long-term study⁸⁷ (16 months) revealed that apomorphine bolus decreased "off" periods by 58% (from 6.9-2.9 hours) whereas patients receiving continuous infusion, supplemented with bolus doses as necessary, had a 54% decrease in "off" period (from 9.9-4.5 hours). Only 7% of patients presented with psychiatric manifestations. In a longer study⁹² (2.7 years) of 19 patients with PD and severe fluctuations patients were treated with waking day continuous SC apomorphine supplemented with bolus doses as needed. Levodopa was withdrawn slowly approximately 3.3 months and a 65% decrease in dyskinesia severity, 85% decrease in frequency and duration of dyskinesia, and a reduction in "off" time from 35% to only 10% were observed. Decreasing the L-dopa dose lead to a further reduction in "off" time. The beneficial effects of apomorphine have been reported up to 5 years.^{86,93} Common adverse effects of apomorphine are nausea and vomiting which can be prevented by

Table 1 - Chemical and pharmacological specificity of dopamine agonists in vitro.

Dopamine agonist	Structure	D1	D2	D3	5-HT	α_1	α_2	β
Apomorphine	Aporphine	++	++	++	0/+	0/+	++	NA
Bromocriptine	Ergot derivative	*	++	+	++	+++	++	NA
Cabergoline	Ergot derivative	0/+	+++	+++	++	++	++	NA
Lisuride	Ergot derivative	0/+	++++	NA	+++	+++	++++	NA
Pergolide	Ergot derivative	0/+	++++	+++	0/+	++	++	+
Piribedil	Non-ergoline derivative	+	+++	+++	NA	NA	NA	NA
Pramipexole	Non-ergoline derivative	0/+	+++	++++	0/+	0/+	++	0
Ropinirole	Non-ergoline derivative	0	++++	++++	0	0	0	0

* = antagonist, 0 = no activity, + = low affinity, ++ = mild affinity, +++ = moderate affinity, ++++ = maximum affinity, NA- information not available, α_1 & α_2 - alpha-adrenergic, β - beta-adrenergic, D1 - dopamine one, D2 - dopamine 2, D3 - dopamine 3, 5-HT - serotonin

Table 2 - Pharmacokinetic properties of dopamine agonists.

Drug	Maintenance Dosage	F %	Tmax hours	PB %	Elimination t _{1/2} hours	Unchanged in urine %
Apomorphine	3-30 mg sc in 3-10 divided doses or 15-60 μ g/kg/hour sc infusion	10-20 SL	0.3-1.0	96	0.5-1.0	0
Bromocriptine	5-10 mg oral tid	6	0.5-2.5	90-96	3-7	2-5
Cabergoline	2-6 mg oral od	50-80	0.5-4.0	40	63-110	<4
Lisuride	0.2-1.5 mg oral tid 0.3-0.6 mg SC tid 0.3-1.0 mg/h infusion	10-20	0.2-1.2	70	1.3-2.5	0.05
Pergolide	0.5-1.0 mg oral tid	20-60	1-3	95-96	27	NA
Piribedil	120-240 mg oral in 2-10 divided doses	Low	-	-	-	-
Pramipexole	0.5-1.0 mg oral* tid	>90	1-3	15	8-12	90
Ropinirole	1-6 mg oral tid	50	1-2	20-40	6	5-10

* - dose expressed in terms of base (multiply by 1.42 for equivalent strength in terms of salt).
F - oral bioavailability, od - once daily, PB - protein binding, SC - subcutaneous, SL - sublingual, T_{max} - time to peak plasma concentration, t_{1/2} - half-life, tid - three times daily, NA - information not available.

Table 3 - Clinical efficacy of dopamine agonists in comparison to placebo or levodopa in early Parkinson's disease.

Drug	n of patients receiving DA treatment vs. PL or LD or combination of LD & DA	Duration of study (months)	Completed study % vs. [PL or LD]	Responders % vs. [PL or LD or combination of DA & LD]	Mean change in UPDRS motor score vs. [PL or LD]	Mean change in UPDRS ADL score vs. [PL or LD]	Patients requiring LD rescue % vs. [LD]	Motor complications % vs. [LD or combination DA + LD]
Bromocriptine ¹²	62 Bro (31 mg ^a) 64 LD (471 mg)	60	0 [48 (LD)]	8 ^b [38 (LD)]	-	-	71	37 ^c /0 ^d , ^e [41 ^c /55 ^d (LD)]
Pergolide ²¹	53 Per (2.1 mg) 64 PL	3	81 [88 (PL)]	57 ^f [17 (PL)]	-7.5 ^f [-1.7 (PL)]	-2.3 ^f [+0.1 (PL)]	-	-
Lisuride ³⁴	30 Lis (1.2 mg) 30 LD (668 mg) 30 LD (484 mg) + Lis (1.1 mg)	48	17 [83 (LD)] [90 (LD + Lis)] ^e	33 [25 (LD)] [28 (LD+Lis)]	-	-	80	0 ^c ,g/0 ^d ,g (52 ^c /64 ^d (LD)) [7 ^c /19 ^d (LD+Lis)] ^f
Pramipexole ⁵²	164 Pra (3.8 mg) 171 PL	6	83 [80 (PL)]	NR	-4.7 ^h [+1.3 (PL)]	-1.8 ^h [+0.4 (PL)]	-	-
Ropinirole ⁷⁵	179 Rop (16.5 mg) 89 LD (753 mg)	60	47 [51 (LD)]	48 [58 (LD)]	-0.8 ⁱ [-4.8 (LD)]	+1.6 [0 (LD)]	66 [36 (LD)]	20 ^d ,f [46 (LD)]
Cabergoline ⁴³	208 Cab (3 mg) 204 LD (500 mg)	48	46 [47 (LD)]	NR	-6.1 [-8.7 (LD)]	-2.4 [-2.7 (LD)]	65 [48 (LD)]	22 ^k [34 (LD)]
*Piribedil ⁶⁷	61 Pir (150 mg) 54 PL	6	85 [89 (PL)]	62 ^k [40 (PL)]	-10 ^g [-6.7 (PL)]	-	-	-

n - number, * - adjunct to levodopa therapy, Bro - bromocriptine, LD - levodopa, PL - placebo, Per - pergolide, Lis - lisuride, Rop - ropinirole, Cab - cabergoline, Pra - pramipexole, Pir - piribedil, a - at 3 years, b - p<0.01 versus levodopa at one year, c - wearing-off, d - dyskinesia, e - p<0.002 versus levodopa, f - p<0.001 versus levodopa or placebo, g - p<0.05 versus levodopa or placebo, h - p<0.0001 versus placebo, i - p<0.01 versus levodopa or placebo, j - median, k - p<0.02 versus levodopa or placebo, ADL - activities of daily living, DA - dopamine agonist, NR - not reported, UPDRS - unified Parkinson's disease rating scale, vs - versus

Table 4 - Clinical efficacy of dopamine agonists in comparison to placebo or levodopa in advanced Parkinson's disease.

Drug	n of patients receiving DA treatment vs. [PL]	Duration study (months)	Completed study % vs. [PL]	Reduction in "off" time % vs. [PL]	Mean change in UPDRS motor score vs. [PL]	Mean change in ADL score vs. [PL]	LD (mg) (percentage LD sparing) vs. [PL]	Incidence of dyskinesia % vs. [PL]
^a Bromocriptine ⁹⁴	84 Bro (22.6 mg) [83]	9	80 [60]	21 [8]	-6 ^b [-3]	-1 ^c [-1]	-	45 [27]
^a Pergolide ²⁷	189 (Per 2.9 mg) [187]	6	84 [82]	32 ^d [4]	-	-9.7 ^d [-2.8]	235 mg (-26%) ^d [51 mg (-5%)]	62 [25]
Lisuride ³⁵	20 (Lis 2.4 mg)	2	85	52	-	-	920 mg (-11%)	0
^a Pramipexole ⁵⁴	181 (Pra 3.4 mg) [179]	8	83 [78]	31 ^d [7]	-5.7 ^c [-2.8]	-1.3 ^c [-0.1]	229 mg (-27%) ^e [43 mg (-5%)]	61 [41]
^a Ropinirole ⁷⁶	95 (Rop 3-24 mg) [54]	6	78 [65]	12 ^f [5]	-	-	242 mg (-31%) ^d [51 mg (-6%)]	34 [13]
^a Cabergoline ⁹⁵	123 (Cab 2-10 mg) [65]	6	89 [83]	-	-2.7 ^f [-1.1]	-2.9 ^f [-0.6]	175 mg (-18%) ^d [26 mg (-3%)]	NR

a - adjunct to levodopa therapy, b - p<0.01 vs. levodopa or placebo, c - p<0.02 vs. levodopa or placebo, d - p<0.001 vs. levodopa or placebo, e - p<0.0001 vs. placebo, f - p<0.05 vs. levodopa or placebo, Bro - bromocriptine, Per - pergolide, Lis - lisuride, Pra - pramipexole, Rop - ropinirole, Cab - cabergoline, ADL - activities of daily living, DA - dopamine agonist, LD - levodopa, NR - not reported, PL - placebo, UPDRS - unified Parkinson's disease rating scale, vs. - versus, n - number.

pretreatment with domperidone.⁹⁶ Neuropsychiatric adverse effects occur with long-term use but the incidence is lower than with other DA.⁸⁷ Dyskinesias also occur with continued use.⁹⁶ Apomorphine appears to interfere with the absorption of L-dopa necessitating care in the timing of administration.⁹⁷

In conclusion, the pharmacological profiles (specificity) of DA translate into different clinically important effects. Irrespective of the chemical structure (ergot or non-ergoline derivative) DA (bromocriptine, pergolide, lisuride, cabergoline, pramipexole, piribedil and ropinirole) in monotherapy improve the motor function in early PD by 10-30% compared to placebo, but this result is inferior to that of L-dopa. On the other hand, DA reduce and delay the onset of motor response fluctuations by almost 25% compared to L-dopa. In advanced PD, DA as add-on to L-dopa improve disability approximately by 20-30%, reduce 'off' time by 15-30% and have a significant L-dopa sparing effect of up to almost one third. However, low response rates, high incidence of adverse effects and tolerance limits the use of most of them. Although the adverse reaction profile of non-ergoline DA is substantially better than their ergot counterparts, hallucinations, somnolence and sleep attacks can be a matter of concern. However, these adverse effects seem to be a class effect of DA rather than a side effect of non-ergoline DA since they have been reported with almost any DA (bromocriptine, cabergoline, lisuride, pergolide, piribedil, ropinirole and pramipexole)^{57-59,98} and L-dopa⁵⁸ as well. In combination with L-dopa, DA may potentiate the dopaminergic side effects of L-dopa and may cause or exacerbate pre-existing dyskinesias, which can be controlled and reduced by lowering the L-dopa dose. Despite of being marketed in several countries, the experience with piribedil in early and advanced PD is still limited. The experience with aporphines (apomorphine) is restricted to advanced PD, where the drug is used as add-on to L-dopa or as rescue therapy for severe "off" periods during L-dopa therapy. Although at long-term the results look promising (for example, 54% decrease in "off" time) the experience is too limited and often anecdotal.

Other evidence that could justify the use of DA in PD is their potential neuroprotective effect since they theoretically generate less hydrogen peroxide and fewer free radicals, and help to protect dopaminergic cells.

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